DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES ADVISORY COUNCIL

MINUTES OF THE 57th MEETING

September 13, 2005
8:30 a.m. to 4:00 p.m.

I. CALL TO ORDER

The 57th meeting of the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council was held on September 13, 2005, at the National Institutes of Health (NIH) Campus, Building 31, Conference Room 6. The meeting began at 8:30 a.m.

Attendance

Council members present

Dr. Graciela S. Alarcon
Dr. Gena R. Carter
Dr. Bevra H. Hahn
Ms. Victoria B. Kalabokes
Dr. Brian L. Kotzin
Dr. Martin J. Kushmerick
Dr. Cato Laurencin
Dr. Richard T. Moxley
Dr. Robert J. Oglesby (Ex Officio)
Dr. Jack E. Parr
Dr. Lawrence G. Raisz
Ms. Mary Elizabeth Replogle
Dr. Raymond Scalettar
Dr. John R. Stanley
Dr. Steven L. Teitelbaum
Ms. Sharon F. Terry
Dr. Jouni J. Uitto

Council members not present

Dr. Francesco Ramirez
Dr. Randy Rosier

Staff and Guests

The following National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) staff and guests attended:

Staff

Dr. Deborah Ader
Dr. Janet Austin
Ms. Susan Bettendorf
Mr. Gahan Breithaupt
Dr. Eric Brown
Ms. Kelli Carrington
Ms. Anne Connors
Ms. Valerie Green
Dr. Elizabeth Gretz
Dr. Steven J. Hausman
Ms. Lisa Hill
Dr. Stephen I. Katz
Dr. Cheryl A. Kitt
Dr. Gayle Lester
Ms. Leslie McIntire
Mr. Robert Miranda-Acevedo
Dr. Alan N. Moshell
Ms. Melinda Nelson
Dr. Glen Nuckolls
Dr. James Panagis
Ms. Wilma Peterman
Dr. Paul Plotz
Ms. Karin Rudolph
Dr. Susana A. Serrate-Sztein
Dr. William Sharrock
Ms. Helen Simon
Dr. Madeline Turkeltaub
Dr. Bernadette Tyree
Dr. Yan Wang

Guests

Ms. Roberta Biegel
Ms. Kina Forrest
Ms. Christy Gilmour
Ms. Joan Goldberg
Ms. Patricia Brandt Hansberger
Dr. Liz Horn

Mr. Robert Jasak
Ms. Susan Whittier
Other NIAMS staff members and guests also were present. Dr. Stephen Katz, Director of the NIAMS, chaired the meeting.

II. CONSIDERATION OF MINUTES

A motion was made, seconded, and passed to accept the minutes of the 56th Council meeting, held on June 14, 2005.

III. FUTURE COUNCIL DATES

Future Council meetings have been confirmed for the following dates:

January 17, 2006
May 23, 2006
September 26, 2006
February 27, 2007
June 12, 2007
September 27, 2007

IV. DIRECTOR'S REPORT AND DISCUSSION

NIAMShorttakes

The NIAMShorttakes, prepared by Mr. Ray Fleming, focused on a dimension of the NIH Roadmap for Medical Research related to infrastructure for translational and clinical sciences. The Shorttakes also provided a detailed review of recent research advances and other updates; Dr. Katz encouraged Council members to read the Shorttakes, which is available online.

Hurricane Relief

The NIH has contributed to hurricane relief efforts in a number of ways, such as sending clinicians and social workers to Louisiana and Mississippi, deploying a medical team to Meridian, MS; and creating and activating a national coordination/referral center for specialty medical consultations. In addition, 100 beds have been made available at the NIH Clinical Center for patient transfers. The NIH has established a Web site that includes post-Katrina information for investigators at affected institutions, many of whom are being invited to come to the NIH and other academic health centers in an effort to provide homes for residents, fellows, and others who have been displaced as a result of the hurricane.

Outgoing Council Members

Dr. Katz acknowledged and thanked the following outgoing Council members: Ms. Victoria Kalabokes, Chief Executive Officer of the National Alopecia Areata Foundation; Dr. Cato Laurencin, Lillian T. Pratt Distinguished Professor and Chairman, Department of Orthopaedic Surgery, University of Virginia; Dr. Richard Moxley, Director of the Neuromuscular Disease Center, University of Rochester; Ms. Mary Elizabeth Replogle, a consultant; and Dr. Francesco Ramirez, Chief Scientific Officer at the Hospital for Special Surgery. Dr. Katz also introduced Council member Dr. Bevra Hahn, Professor in the Department of Medicine at the University of California, Los Angeles, who was attending her first Council meeting.

Personnel Changes

Ms. Felecia Taylor, Secretary to the Director of the NIAMS Extramural Program, has accepted a position in the NIH Ethics Office after 14 years of service to the Institute. Ms. Reva Lawrence, an epidemiologist in the NIAMS extramural program who has been with the Institute since 1978, is retiring. Dr. Helen Lin, who has been serving as a Special Volunteer in the NIAMS Extramural Program Review Branch, has officially joined the Branch as a Scientific Review Administrator. Ms. Helen Simon, Director of the NIAMS Office of Program Planning, has d a new role as Senior Advisor for Program Coordination in the NIAMS. Ms. Valerie Green, Senior Administrative Officer, Office of the Director, has been selected as the new Chief of the Administrative Management Branch for the Office of the Director and the Extramural Program.

Update on Budget and Congressional Activity

Both the House and Senate Appropriations Committees have completed markup of the fiscal year 2006 appropriations bills for the Department of Labor , Health and Human Services, Education and Related Agencies. The House bill includes $28.5 billion for the NIH, which essentially is the same as the President's request; this amount represents a 0.4 percent increase for the NIH. The NIAMS allocation is $513.1 million, a 0.5 percent increase over the FY2005 comparable amount. The Senate bill provides $29.4 billion for the NIH, an almost $1 billion increase that is 3.5 percent higher than the FY2005 comparable level. The amount proposed for the NIAMS by the Senate is $525.8 million, which is an increase of $12.7 million, or 2.9 percent, over FY2005. The differences between these two bills must be reconciled before the final appropriations bill can be passed. If this does not occur before October 1, the NIH will begin the fiscal year operating under a Continuing Resolution.

The House Energy and Commerce Committee held a hearing on July 19, 2005, to discuss draft legislation to reauthorize the NIH. This draft legislation contains provisions that would: (1) group existing Institutes and Centers into two major categories, mission-specific and science-enabling; (2) delineate new authorities for the NIH Director; (3) establish the Division of Program Coordination,

Planning, and Strategic Initiatives at the NIH level; (4) establish an electronic coding system and require a biennial report to Congress; and (5) authorize grants for certain demonstration projects.

Highlights of Recent Scientific Advances

- In a 16-center, long-term study of menopausal women with lupus, investigators led by Drs. Jill Buyon (New York University School of Medicine) and Michelle Petri (Johns Hopkins University) found that hormone replacement is not associated with severe lupus flares. Women with lupus who were treated with hormone replacement therapy (HRT) were approximately 20 percent more likely to develop a mild to moderate disease flare; however, none of these flares resulted in the need for high-dose steroids or hospitalization.

- Dr. Maria Garcia Popa-Lisseanu at Ben Taub General Hospital in Houston and colleagues identified some of the barriers that keep economically disadvantaged and ethnically diverse lupus and arthritis patients from complying with their prescribed medical treatments. These barriers include fear of side effects, belief that the medicine is not working, problems with the health system environment, and medication cost. Effective measures need to be developed to address these challenges.

- Dr. Francis Keefe and colleagues at Duke University Medical Center studied the use of spouse-assisted coping skills training and exercise training to improve physical fitness, pain coping, and self efficacy in patients with osteoarthritis of the knee. Results suggest that a combination of both types of training leads to more improvement than could be achieved with either intervention alone, further reinforcing the concept that patients who take control of their disease tend to have better outcomes. These findings likely can be extrapolated to other chronic diseases.

- In a paper published recently in the *New England Journal of Medicine*, Dr. Dennis Black of the University of California, San Francisco, and colleagues found that administering alendronate following parathyroid hormone therapy for the treatment of osteoporosis maintains the positive effects of the initial parathyroid hormone therapy.

- Drs. Terry Lechler and Elaine Fuchs at the Howard Hughes Medical Institute at Rockefeller University have used imaging techniques and antibodies to show evidence of asymmetric cell division in mammalian skin cells. This research provided a view of how skin is able to create layers of different cell types at the same time as it is forming a protective barrier. The next step in this effort is to determine which genes are necessary for this process to occur.

- Dr. Tariq Haqqi and colleagues at Case Western Reserve University have shown that, in tissue samples of human cartilage affected by osteoarthritis, pomegranate extract has antioxidant and anti-inflammatory properties that slow human cartilage deterioration. The mechanism involves an interleukin-1β protein that creates an overproduction of inflammatory molecules, including some of the matrix metalloproteinases. It will be important to determine whether pomegranate extract promotes cartilage repair and whether pomegranate extract might also be effective in treating rheumatoid arthritis.

Highlights of Recent and Upcoming Activities

The Institute has put a moratorium on new Program Projects; however, existing ones will be allowed two cycles at most. Those that already have had two or more cycles of funding will need to be transitioned to other forms of funding.

The NIAMS has entered into a Memorandum of Understanding with the American Skin Association and the Orthopedic Research and Education Foundation to support an individual fellowships (F32) similar to those focused on epidemiology, outcomes, and clinical research in skin disease that were created in conjunction with the Herzog Foundation several years ago.

In recent years, the use of genetically altered, or knockout mice, has become critically important. Individual laboratories have been engineering these mice at a great expense for specific projects. Some of the many hundreds of knockout mouse strains that have been created in the private sector may soon become available to the NIH research community in a public database, which would represent an extremely valuable resource.

There has been a long-recognized shortage of pediatric rheumatologists, and the NIAMS has awarded a pediatric rheumatology training program at the Children's Hospital of Pittsburgh in addition to the NIAMS-funded pediatric training program at Children's Hospital Medical Center of Cincinnati. The NIAMS also funds a training program for both adult and pediatric rheumatologists at Stanford University.

In terms of activities at the NIH level, Dr. Katz reminded participants that shortly after the inception of the NIH Roadmap for Medical Research, he was one of the major leaders of the Roadmap initiative of Re-Engineering the Clinical Research Enterprise. Strategies are needed to improve efforts in translational research and to encourage training in the conduct of clinical/translational research. Within the next month, the NIH plans to unveil a new award mechanism that will help institutions create an academic home for translational and clinical science.

At the NIH Directors Retreat, which was held during the week before this Council meeting, discussions focused on the NIH Office of Program Coordination,

Planning, and Strategic Initiatives; an update on NIH reauthorization; and the NIH's external constituencies. There also was a focus on the Center for Scientific Review, led by the Center's Director, Dr. Antonio Scarpa, who has a goal of shortening the interval between submission and review to decrease the cycle time by 4 months. Two internal issues also were addressed: (1) is there a need for a more thematic approach for NIH science, and (2) what is the role of special initiatives, and what is the balance between small, large, and "mega" scale scientific projects?

The NIH recently announced the final regulations related to conflict of interest.

The White House Office of Science and Technology Policy (OSTP) has issued a broad request for information from the scientific community regarding the possibility of listing more than one Principal Investigator (PI) on a single research project. On a continuous basis, the NIH is seeking feedback from all of its communities on issues such as allocation of funds, and apportionment of the budget to Co-PIs on research projects. Council members were encouraged to visit the NIH Web Site and provide their input.

In discussion, Ms. Kalabokes asked when the draft NIH reauthorization legislation would be made available. Dr. Katz indicated that a second draft of the bill has been shared with various communities. There was considerable discussion of the NIH response to the bill at the NIH Directors Retreat, and the NIH already has initiated activities covered in the bill (e.g., establishing the Office of Portfolio Analysis and Strategic Initiatives).

V. A STRONG FOUNDATION: BUILDING A HOME FOR THE CLINICAL AND TRANSLATIONAL SCIENCES

Dr. Barbara Alving, Acting Director of the National Center for Research Resources (NCRR) at the NIH, is leading the effort at the NIH to build a strong foundation and home for clinical and translational sciences and address the competing priorities for resources at the NIH. Challenges facing the clinical research enterprise include: (1) difficulty in recruiting and retaining clinical researchers; (2) increasing regulatory burden and overhead costs; (3) fragmented training programs; and (4) limitations/barriers due to NIH funding mechanisms, reviews, and program structures.

Although academic health centers are experiencing an explosion in clinical service demands, reductions in financial margins have limited the time available for research and the mentoring of clinical/translational scientists. A marked increase in the number of faculty members at many institutions has led to a "dilution" effect, with a decreasing value attached to translational and clinical sciences. The complexity of knowledge necessary for becoming an effective clinical/ translational scientist is not easily acquired, and young clinical faculty

members hoping to conduct translational work often have difficulty finding a "home" for their aspirations.

To strengthen academic health centers' clinical sciences infrastructure, the NIH is helping to build training programs, a K30 curriculum, General Clinical Research Centers-focused (GCRC), and disease centers. Although there are many ongoing efforts at academic health centers in this regard, they generally are not linked; rather they have been layered on top of each other. The missing pieces needed to adopt a systems biology approach to creating a home for clinical and translational sciences include biostatistics, informatics, and regulatory advice; Institutional Review Boards; a clinical research design incubator; translational cores; input from the NIH Rapid Access to Interventional Development Program, National Electronic Clinical Trials and Research Network, and National Clinical Research Associates Program; and degree-granting capabilities/opportunities. The NIH approach will be tailored according to the needs and capabilities of each academic health center.

Transforming goals are to: (1) provide the academic home and integrated resources needed to advance the new intellectual discipline of clinical and translational sciences, (2) create and nurture a cadre of well-trained investigators, and (3) advance the health of the nation by transforming patient observations and basic discovery research into clinical practice. In 6-8 years, it is hoped that development of this institutional home for clinical and translational sciences will be complete. Components will include research design, statistics, and regulatory affairs; biomedical informatics; a career development program (curriculum, slots); inpatient, outpatient, and community subject accrual sites; core laboratories; a pilot project program; and a governance core.

Providing program flexibility will be key—a flexible configuration must be tailored to the needs and strengths of individual institutions, with a flexible location/configuration, sufficient resources to develop the needed infrastructure, adaptable size, and support for local creativity and adaptability. New programs will support different experimental models and approaches; these flexible programs will have adjustable sizes for different needs.

A meeting entitled "Enhancing the Discipline of Clinical and Translational Sciences" was held on May 23, 2005, in Crystal City, VA, to discuss this effort. Presentations and reports from working groups at the meeting are available online at: http://www.ncrr.nih.gov/clinicaldiscipline.asp. An RFA for institutional clinical and translational science work has been developed and will be announced on October 12, 2005. Planning grant initiatives also will be released, and a technical workshop is planned for October 17, 2005, so that potential grantees can receive additional information.

In discussion, Dr. Katz reminded Council members and other attendees that for this effort to be successful for every NIH Institute, it must accelerate and facilitate

the research that is ongoing in each area. Dr. Hahn asked about regulatory obstacles. Dr. Alving noted that the first step involves 4-7 Institutional Clinical and Translational Science Awards (CTSAs) that will emphasize synergy between the academic centers and their partners who are participating in CTSAs. Annual meetings are planned, and a strong emphasis will be placed on the need for adapting and integrating best practices and standards for informatics.
Dr. Katz noted that there is an effort to harmonize some of the various government agencies in terms of adverse event reporting and other activities, first within the NIH, then within other government agencies, and then with the private sector.

Dr. Moxley asked how Dr. Alving views the interaction between existing GCRCs and this program, and whether there is an opportunity or need to transition the existing GCRCs into this model. This is a critical issue for the long-term planning efforts at academic centers. Dr. Alving noted that the key is transition. It is envisioned that academic health centers and their partners that have GCRCs could apply for this CTSA, and this could be folded in or transitioned, so that there are not parallel tracks.

Council member Dr. Brian Kotzin, Vice President of Development at Amgen, asked for a description of the input that went into forming this initiative on the part of the biotechnology and pharmaceutical industries. He also asked about the interface between academic clinical centers and industry. Dr. Alving explained there are ongoing conversations with industry in terms of partnering throughout the NIH, and allowing and encouraging the flexibility of partnerships with industry. Many of the challenges in this regard are related to intellectual property and the time needed for the NIH to take action because of regulatory issues. Dr. Katz added that input from industry was solicited and considered from the initial stages of this initiative.

Council member Dr. Jack Parr, of Medical Technology Development, Inc., asked how this program would fit in with obtaining clearance from the U.S. Food and Drug Administration (FDA) to market, demonstrate cost effectiveness, and broaden indications for medical devices. Dr. Alving responded that this could work in a variety of ways. The NIH receives applications for investigational new drugs quite frequently, from both extramurally funded studies as well as from the intramural programs. These usually are to develop new uses for marketed drugs from the FDA. This effort would improve on partnerships, provide support, and make the entire process easier.

Dr. Lawrence Raisz, Council member and Director of the University of Connecticut Center for Osteoporosis, asked whether this initiative will involve a mix of centers and training grants or a mix of large and small institutions. Dr. Alving indicated that this is not yet clear; however, this will be a gradual process and there is a plan in place to provide funding. Dr. Raisz noted that the transition

could be a fairly long one for some institutions; Dr. Katz agreed, noting that the plan is for this transition to take 6-8 years.

Council member Dr. John Stanley, Milton B. Hartzell Professor and Chairman of the Department of Dermatology at the University of Pennsylvania School of Medicine, noted that many institutions may already be trying to provide these clinical and translational homes. He asked whether any institutions can be identified as using best practices and emulated. Dr. Alving noted that Vanderbilt University and the University of Pittsburgh are examples of ongoing efforts that have been successful. Dr. Katz reiterated that there will not be a prescription in terms of the RFA that will be released; many approaches could be used. The NIH is looking for broad community input in building these research homes. One important challenge will be ensuring that various research areas are well represented.

VI. NIAMS-SUPPORTED PATIENT REGISTRIES

Dr. Alan Moshell, Director of the NIAMS Skin Diseases Branch, noted that a number of registries that now are funded by the NIAMS were established before it became a separate NIH Institute. For example, the Epidermolysis Bullosa (EB) registry was Congressionally mandated when the NIAMS was part of the National Institute of Diabetes and Digestive and Kidney Diseases. Most registries supported by the NIAMS are funded via open competition using contract mechanisms.

The EB registry was supported for more than 15 years through three successive 5-year contracts; NIAMS funding ceased in 1999. No repository was funded by a registry contract; although the registry's participating investigators did collect specimens on their own. This registry had fairly broad objectives, because at the time this registry was created, the exact cause of EB was unknown. The registry was formed to help identify diagnostic criteria for the various forms of EB and then act as an impetus for determining the basic underlying etiology of the EB diseases as well as determining prevalence, natural history, etc. The success of the EB registry resulted in two competitions via the contract mechanism for additional registries. The first, in 1994, funded the following five registries: (1) Juvenile Rheumatoid Arthritis, (2) Neonatal Lupus, (3) Scleroderma (NIAMS funding will be terminating in 2006), (4) Ichthyosis (NIAMS funding terminates in 2005), and (5) Juvenile Dermatomyositis (NIAMS funding terminated in 2000). Although NIAMS funding has terminated or will terminate soon for some of these registries, they remain available to the community in one form or another because of funding from other sources.

A second competition in 2000 funded the following registries: (1) Early Rheumatoid Arthritis in African Americans, (2) Antiphospholipid Syndrome, (3) Alopecia Areata, and (4) Myotonic Dystrophy and Fascioscapulohumeral Dystrophy. These registries are still active and may or may not be renewed at the

end of their respective 5-year funding periods. The following three registries, which were not funded as a result of broad agency announcements but through grants, subsequently were converted into contracts: (1) Lupus, (2) Rheumatoid Arthritis, and (3) Fibromyalgia (NIAMS funding terminates in 2005).
Some of the registries funded by the NIAMS have repositories; others do not. They are all slightly different (e.g., some involve multiple clinical sites, others single sites; some involve Internet registration, others do not), and most are involved with a voluntary agency or agencies. The overall objectives and accomplishments vary and include the establishment of diagnostic criteria, natural history studies, gene discovery, support for interventional studies, and providing participants and/or specimens for basic research studies.

Sunsetting these registries was not directly addressed when the registry program was started. NIAMS staff currently are examining registries to address what happens when NIAMS dollars are no longer available—the intent is to avoid creating future registries that cease to exist once NIAMS funding ends. Registries should fill a need in the community and their value should be demonstrable by continued community support for and use of the registry itself. The NIAMS has been considering whether now is the appropriate time to release a new solicitation for registries, and in the interim, other mechanisms have been identified or developed that can support registries. A broad agency announcement may not be the most appropriate approach to funding registries in light of these other mechanisms.

In discussion, Council member Dr. Jouni Uitto, Professor and Chair of the Department of Dermatology and Cutaneous Biology at Jefferson Medical College, asked about the success of registries other than the EB registry. Dr. Moshell explained that the majority of the registries are in the area of rheumatic diseases, and many have enjoyed similar levels of success as the EB registry (Dr. Moshell reminded Council members that these newer registries have more limited objectives and have been in existence for shorter periods of time).

Dr. Susana Serrate-Sztein, NIAMS Branch Chief for Rheumatic Diseases Branch, noted that the Institute has internal criteria that are used to evaluate the registries on a regular basis to determine their level of success. To be funded by the NIAMS, registries need to be designed so that a particular research objective can be met. For example, a registry could be built in such a way that the measurement and specimens would be useful for genetic studies; it could be constructed so that the information and specimens could be used for the identification of patient subsets; or it could be developed to obtain some critical information on a patient population that was not otherwise available. When evaluating registries, consideration is given to progress based on the number of patients enrolled, community input, and a variety of other factors. Most NIAMS-funded registries have internal advisory committees, and success can be examined through annual progress reports and other measures. Although there is a concern that the costs associated with maintaining registries could escalate so rapidly that they would

exceed the available resources, there are cost-effective approaches to maintaining registries. There also are legal issues, such as determining who owns the collections and who is responsible for ensuring that they are used in the spirit for which the consent forms were obtained. Institutions need to be made aware of how long they will be keeping and maintaining collections, and that they must maintain open access to the collections for the scientific community.

Council member Dr. Steven Teitelbaum, Professor at the University of Washington School of Medicine, noted that a critical issue is accountability for the individual centers. Dr. Serrate-Sztein explained that each registry's external advisory committee is responsible for guiding the registries in this regard. In addition, progress is measured and monitored on a regular basis. Dr. Teitelbaum asked whether any registries have been discontinued because of poor performance in meeting their goals. Dr. Katz responded that NIAMS Program Directors are critical of what certain programs, including NIAMS-funded registries, are delivering, and have had to tell certain groups that their registries will not continue to be funded by the Institute because of inadequate progress. It is a challenge, because there are hundreds of rare diseases that have groups who would like to have a registry associated with them. One requirement for each NIAMS-funded registry is that there be a study attached to the registry.

Dr. Teitelbaum asked about exit strategies for registries that lose their funding. Dr. Serrate-Sztein noted that a driving force in whether a registry in this situation continues is whether the work being done could be done as an R01.

Dr. Raisz commented that establishing registries that come and go on a contract basis may not be an appropriate activity for the NIAMS. Dr. Graciela Alarcon, a Council member and the Jane Knight Lowe Chair of Medicine in Rheumatology in the Division of Clinical Immunology and Rheumatology at the University of Alabama at Birmingham, added that there is a concern that the registries in some cases are used by investigators who receive funding for the registry rather than by the greater scientific community.

Dr. Gena Carter, a Council member, radiologist, and patient advocate, asked if consideration was being given to ending funding for registries at the NIAMS level. Dr. Katz asked whether there is a compelling reason to have new solicitations for registries, regardless of mechanism. There is greater oversight when there is a contract, but the issue is the importance of these registries in the context of other activities. Council member Ms. Replogle indicated that registry groups do promote more research on affected patients than would happen otherwise, and there are many other benefits associated with repositories/registries.

Dr. Teitelbaum asked if there is a funding mechanism to have groups such as the Genetic Alliance (whose President and CEO is Council member Ms. Sharon Terry) funded by the NIH, because these types of groups are committed forever,

and it is unlikely that communities will lose interest in these groups. Dr. Katz indicated that such a mechanism does not exist at present. Dr. Teitelbaum noted that groups such as the Genetic Alliance have a much stronger foundation and long-term commitment than operations run by individual investigators or universities.

Dr. Hahn mentioned that some registries have been effective in gathering materials that can be used by a large number of investigators to generate data. One possibility may be to encourage more competition for registry funding and more stringent guidelines that include exit strategies. It should be difficult to obtain funding for a registry because of strict criteria. Eliminating registries from being funded by the NIAMS might not be the best solution.

Council member Dr. Jack Parr, of Medical Technology Development, Inc., suggested that guidelines for establishing registries be developed to assist groups who want to form a registry. The guidelines should include information on the steps needed to apply for NIH funding. One possibility under this scenario would be to have the NIH provide start-up funds only, then have the registry be responsible for identifying and securing funds to keep itself running.

VII. NIH CONFLICT OF INTEREST REGULATIONS

Ms. Holli Beckerman Jaffe, Director of the NIH Ethics Office, presented a policy overview of NIH conflict of interest regulations. As special Government Employees (SEGs), Council members are specifically excluded from the application of these rules. The NIH conflict of interest statutes apply to Council members, but these specific rules do not. Interim final rules were released in February, with a request for comment. Between the Department of Health and Human Services (DHHS) and the NIH, more than 2,000 comments were collected. The DHHS evaluated the February guidelines and has made certain revisions, which were guided by three principles: (1) the public must be assured that research decisions made at NIH are based on scientific evidence and not by inappropriate influences; (2) senior management and those who play an important role in research decisions must meet a higher standard of disclosure and divestiture than those who are not decisionmakers; and (3) to advance the science and stay on the cutting edge of research, NIH employees must be allowed interaction with professional organizations, participation in public health activities, and genuine teaching opportunities.

For the purposes of this policy, senior employees include: (1) the NIH Director and Deputy Director, and senior staff within the Office of the Director who report directly to the NIH Director; (2) the Directors, Deputy Directors, Scientific Directors, and Clinical Directors of each Institute and Center within the NIH; (3) extramural program officials who report directly to an Institute or Center Director; and (4) equivalent employees.

With regard to divestiture of prohibited financial interests, senior NIH employees and their spouses and children may not retain an aggregate interest in a substantially affected organization (SAO) in excess of $15,000 or an aggregate interest in SAO sector funds in excess of $50,000. Exceptions may apply for certain types of financial interests such as pensions, diversified mutual funds (including non-healthcare sector funds), technology transfer, and exceptional circumstances. Other NIH employees continue to be subject to government-wide laws that require divestiture in cases where it is reasonably necessary to resolve a conflict of interest with the employee's official duties, but will not be subject to a blanket prohibition.

Employees who file either a public or confidential financial disclosure report and those nonfilers who serve as clinical investigators identified on an NIH clinical study are required to report the value of any interest in an SAO. Employees who do not meet these criteria generally are not required to disclose interests in SAOs.

Unless an exception applies, NIH employees may not: (1) engage in employment with an SAO, supported research institution, or healthcare provider or insurer; (2) engage in a self-employed business activity with these types of organizations; or (3) teach, speak, write, or edit for compensation for these types of organizations. Employment with related trade, professional, or similar associations; on data and safety monitoring boards; in relation to a Grand Rounds program; as a lecturer in an established course; or on grant or scientific review committees generally is permissible with prior approval. The previously established exceptions remain: teaching a course that requires multiple lectures; clinical practice; writing or editing for a peer-reviewed journal; and presenting a continuing medical education (CME) or CME-like lecture. Outside employment that involves manual or unskilled labor, hobbies, artistic endeavors, or interests unrelated to the health and scientific research of the NIH, such as retail sales, coaching a youth team, scouting activities, clerical work, and building trades are generally permissible without prior approval unless the outside entity is a prohibited source.

With prior approval, employees (including senior-level employees) can accept gifts associated with *bona fide* awards for meritorious achievement. However, if the source of the award can be affected by the employee's duties or those of any subordinates, gifts valued in excess of $200 may not be accepted.

In discussion, Council member Dr. Raymond Scalettar, Clinical Professor of Medicine at George Washington University, noted that in the past, certain NIH employees served as expert witnesses in liability cases. He also asked about injunctions related to mutual funds. Ms. Beckerman Jaffe explained that NIH employees may still serve as expert witnesses; however, at present, NIH employees may not serve as expert witnesses for physicians because they are healthcare providers. It is likely that an exception to this rule will be issued at some point, because it is not likely that testifying for a physician as a medical

expert could affect the integrity of the NIH. With regard to mutual finds, large diversified mutual funds likely will have SAOs in them, but if that is the only way that they are owned, it is permissible. If it is a separate fund for an SAO, however, the total aggregate for health care sector funds cannot exceed $50,000 for senior employees. For other employees, it depends on whether there is a conflict.

Dr. Moxley asked how this policy is affecting NIH's ability to recruit and retain the best and brightest employees. Ms. Beckerman Jaffe explained that because these rules are relatively new, only anecdotal data are available. There are plans to formulate an extensive survey to reach out to those whom the NIH would consider hiring, and it is hoped that more detailed information on recruitment and retention will be available in the future. Ms. Replogle asked about restrictions on owning stock for start-up companies. Ms. Beckerman Jaffe noted that the $15,000 cap applies to any company, public or private, and recognized that valuing stock for privately owned companies is difficult.

Ms. Terry commented that she oversees an umbrella of 600 disease advocacy groups, many of which were adversely impacted by draft rules. Although no one was paid for their participation, many of these groups experienced an exodus of NIH employees from their Boards of Directors and as meeting participants and speakers. This departure did not occur at similar levels across NIH Institutes, and more senior NIH employees tended to continue participating while more junior-level employees were hesitant to ask for permission to participate in these groups. Ms. Terry asked if there are attempts to educate NIH employees on the new rules so that these trends even out. Ms. Beckerman Jaffe explained that efforts are underway to centralize training on the new rules. She noted that Dr. Zerhouni created the NIH Ethics Advisory Committee, comprised of senior individuals from across the NIH who review at-risk activities through a centralized peer review panel, regardless of the Institute of the individual in question.

Dr. Carter asked whether there were specific events that triggered the overhaul to NIH's conflict of interest policy. Ms. Beckerman Jaffe cited a December 2003 article that appeared in the *Los Angeles Times* and a letter from Congress in July of 2003 regarding the NIH awards program. Dr. Katz noted that there were efforts underway to revamp the conflict of interest policy before the increased Congressional and media interest took place. Dr. Stanley noted that many of those he speaks to at the NIH feel that some of the rules are demoralizing and punitive, particularly because it appears to some NIH employees that their colleagues in academia who do similar work adhere to less stringent rules.

VIII. NIAMS IRP ACTING SCIENTIFIC DIRECTOR'S REPORT

Dr. Paul Plotz, Acting Scientific Director of the NIAMS Intramural Program and Chief of the Arthritis and Rheumatism Branch, provided an overview of various activities within the intramural program. The NIAMS intramural research

program can be divided into the following categories: Clinical Research, Clinical and Investigative Orthopaedics, Autoimmunity, Arthritis and Rheumatism, Genetics and Genomics, Molecular Immunity and Inflammation, Cartilage Biology, Muscle Biology, Structural Biology, Protein Expression, and Science and Technology Support. There are a total of 10 PIs in the intramural program, of which 6 are on the tenure track. Dr. Plotz characterized these individuals as a young and vibrant group.

Dr. Plotz briefly touched on a number of ongoing projects within the NIAMS intramural research program by discussing the following series of research questions:

- How should the therapy of rheumatoid arthritis (RA) be assessed, and is the widely used Health Assessment Questionnaire (HAQ) the right measure? HAQ scores in RA patients in remission were found to be higher among those with more longstanding RA, representing chronic, irreversible functional damage. Thus, HAQ as a measure of RA activity is a conflated measure of functional limitations due to active synovitis and functional limitations due to chronic damage. Comparisons of HAQ scores among patients and across studies of different mean durations of RA will be confounded by differences in activity-related versus damage-related functional limitations.

- Can blocking the important downstream mediator of inflammation, IL-1, interfere with the severe inflammation that affects many organs in the genetic "autoinflammatory disease" known as Neonatal Onset Multisystem Inflammatory Disease (NOMID)?

- Why does Pompe Disease, a severe, often fatal muscle disease, respond so poorly to enzyme replacement therapy? It works in other lysosomal storage diseases, but skeletal muscle fibers are highly resistant to therapy. In fast-twitch, glycolytic muscle cells that cannot break down glycogen in Pompe Disease, there is a profound disorder of essentially all vesicular trafficking. Energy starvation in these cells may be responsible and treatable.

- How do immune and inflammatory cells receive and react to signals from the outside? How do these signals get translated into appropriate action, and what can go wrong? It has been found that generation of Stat5 knockout mice results in severe combined immune deficiency. Stat5 is important for multiple steps in a lymphocyte's life, from stem cell differentiation to helper T cell. Stat4 is critical as well. Stat4 knockout mice do not produce interferon gamma and die in response to *T. gondii* infection. If the Stat4 gene is replaced with a Stat4 gene that cannot be serine phosphorylated, the mice will still die of the infectious challenge. Understanding the biochemistry of these types of modifications will provide important insights that may lead to new avenues for therapeutic intervention.

- In autoimmune disease, is antibody development different? Somatic hypermutation can occur outside germinal centers in a normal immune response. Somatic hypermutation can occur outside germinal centers in normal immune responses, not just in autoimmunity.

- What does pyrin, the protein mutated in familial Mediterranean fever, do? Is it an anti-inflammatory molecule? Does it interact with so far unknown PYD-containing proteins? Is it a resistance factor against intracellular pathogens? Mutant pyrin knockin mice are sick and have flagrant arthritis.

- Can cartilage or cartilage-like material be made in a laboratory?

In discussion, Dr. Uitto asked about the future of skin diseases- related research. Dr. Plotz responded that at the NIAMS, the future of intramural skin biology research is undetermined. The NIAMS has a Laboratory of Skin Biology, but its future also is unclear. Dr. Katz added that the National Cancer Institute has a very large dermatology branch, and that there are collaborative programs that cross the span of other interest areas.

IX. NIH ROADMAP: PROMIS

Dr. Deborah Ader, Director of the Behavioral and Prevention Research Program at the NIAMS, provided the Council with an update on a component of the NIH Roadmap known as the Patient-Reported Outcomes Measurement System (PROMIS), which involves the dynamic assessment of patient-reported chronic disease outcomes from a diverse population of patients with chronic diseases. PROMIS falls under the Re-Engineering the Clinical Research Enterprise effort associated with the Roadmap, and attempts to develop a standardized approach to help measure inherently subjective items. The goal of PROMIS is to create highly valid and reliable item banks and associated computerized adaptive testing that will be widely adopted to improve assessment of self-reported symptoms such as pain and fatigue as well as other health-related quality of life domains across chronic diseases. PROMIS has the following three broad objectives: (1) develop and test a large bank of items measuring patient-reported outcomes, (2) create a computer adapted test for efficient assessment of patient reported outcomes across a range of chronic diseases, and (3) create a publicly available, adaptable and sustainable system allowing clinical researchers access to a common item repository and computer adapted tests.

Seven sites—six primary research sites and one statistical coordinating center—have been funded. PROMIS grantees include: Drs. David Cella (Northwestern University), Dagmar Amtmann (University of Washington), Jim Fries (Stanford University), Harry Guess (University of North Carolina), Paul Pilkonis (University of Pittsburgh), Arthur Stone (State University of New York at Stonybrook), and Kevin Weinfurt (Duke University). Overall, more than 100 investigators are involved in PROMIS.

Dr. Ader described how PROMIS fits into the overall NIH Roadmap process. Year 1 network activities include archival data analysis, domain hierarchy mapping, and qualitative item review. She presented the domain hierarchy within the preliminary PROMIS framework, which includes three main overarching domains: (1) physical health (including function, symptoms, and special senses); (2) mental health (including emotional distress, cognitive health, and spiritual health); and (3) social health (including role participation, social support, and societal structure).

Dr. Ader explained that items from various instruments, combined with new items, are used to create an item pool, which is evaluated by expert and patient reviews, focus groups, and cognitive testing. This item pool then is used to develop a questionnaire administered to a large, representative sample. The questionnaire also is available in other languages, including Spanish. Questionnaire results are used to develop an item response theory, which feeds into an item bank, where item response theory-calibrated items are reviewed for reliability, validity, and sensitivity. The item bank then can be used in the development of short form instruments and computer adapted tests, where the questions posed to subjects depend on answers given to previous questions.

Professional societies and groups that are involved in PROMIS include: the American College of Rheumatology Classification and Response Subcommittee, China Academy of Traditional Medicine and Chinese Ministry of Science and Technology, American Physical Therapy Association, Interagency Subcommittee on Disability Research Subcommittee on Medical Rehabilitation/ICF, International Society for Quality of Life Research, and International Society for Pharmacoeconomics and Outcomes Research.

Dr. Katz noted that this initiative has garnered a great deal of enthusiasm from around the NIH because it represents potential advances in the area of chronic diseases and symptoms that are difficult to measure objectively. Dr. Hahn asked if industry has been approached to determine whether there already are some documents or tools that might be helpful. She also asked if there was a plan for sunsetting this type of program. Dr. Ader replied that this type of program could last indefinitely; what needs to last in the long term is some way of sustaining PROMIS to make it accessible and available to clinical researchers. There also will be a need to maintain, update, and fine tune the system periodically because the same questions do not maintain the same level of reliability and validity over long periods of time. Longer-term tasks will not require the same level of activity tied to the current development of PROMIS.

The primary intent of this initiative cannot be accomplished in 5 years; however, the development of item banks for a limited number of domains and an initial computer adapted test could be developed within a 5-year period. The next step then would be to make sure that it becomes used in clinical outcomes research. It

also would be beneficial to develop additional measurement domains and test the system in patient populations that cannot be accessed in the next 5 years. With regard to industry, Dr. Ader commented that to the best of her knowledge, there is no well-established tool similar to the PROMIS system, and a large meeting is planned to provide information on PROMIS to industry and other groups.

Dr. Katz noted that the FDA has significant interest in PROMIS. Ms. Replogle asked if PROMIS could be combined with existing registries to improve information collection in the long-term followup of patients. Dr. Ader noted that the primary goal of PROMIS is to enhance research, but there is a clear opportunity to move into the clinic.

X. NIAMS CONTRACT CONCEPT CLEARANCE

Dr. Cheryl Kitt, Director of the NIAMS Extramural Program, read a statement from Ms. Eileen Webster-Cissel, who was unable to attend the Council meeting. The statement informed Council members that there would be some concepts discussed during the open session of the meeting; others were to be discussed during the meeting's closed session. It is a federal requirement that the NIAMS obtain contract concept clearance from an advisory body, and the Institute has chosen to have the Advisory Council provide input on this process. For concept clearance reviews, the Council is asked to advise the NIAMS regarding the usefulness of the proposed projects. The Council is not asked to set priorities or to make fiscal decisions. Furthermore, the proposed projects are not discussed in detail, only in concept, during the open sessions. If a detailed discussion is needed, all participants involved would be excluded from applying, and a review would have to take place during a closed executive session of the Council. Two proposals were discussed during the open session of this meeting.

Dr. Serrate-Sztein discussed a concept that was previously approved during an open session of the Council in September of 2004. The concept calls for proposals for projects for innovative therapies for rheumatic and skin diseases. The rationale for issuing the solicitation is based on recommendations from the community that identified the need for the NIAMS to have a program of clinical trials involving drug combinations that are not likely to be conducted by industry. The NIAMS has released two previous similar solicitations, both of which generated a number of successful clinical projects involving skin and rheumatic diseases. Some of the studies funded through the previous solicitation have progressed to phase III studies. It is hoped to increase the size of these trials; most of the studies of this type supported by the NIAMS have included fewer than 300 patients. A motion to approve the concept was made, seconded, and passed, with 9 votes in favor and 7 opposed.

In introducing the second proposal entitled: "Assessment and Assistance for NIAMS Clinical Studies," Dr. Madeline Turkeltaub, NIAMS Clinical Research Project Manager in the Office of the Director, Extramural Program, explained that

the NIAMS assesses funded clinical studies and provides technical assistance when needed. The NIAMS is currently supporting approximately 56 clinical trials ranging in size from 10-1,500 participants as well as several large-scale (500-5,000) observational studies. With the focus on translational research, the number of clinical studies is likely to increase. The primary objective of the contract is to provide technical and professional support to clinical research activities conducted through grants or contracts in areas where the staffing and research management resources are limited. Work areas include: (1) technical and administrative assistance for interpretation of NIH/FDA policies and guidelines for specific clinical studies, (2) procedures for assessing and assisting clinical studies, (3) biostatistical and epidemiological support, (4) training, and (5) data safety and monitoring support. A motion to approve the concept was made, seconded, and passed, with 14 votes in favor and none opposed.

XI. CONSIDERATION OF APPLICATIONS

The Council reviewed a total of 650 applications in closed session requesting $142,908,809 and recommended for $137,933,129

XII. ADJOURNMENT

The 57th National Arthritis and Musculoskeletal and Skin Diseases Advisory Council Meeting was adjourned at 4:00 p.m. Proceedings of the public portion of this meeting are recorded in this summary.

I hereby certify that, to the best of my knowledge, the foregoing summary and attachments are accurate and complete.

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Executive Secretary, National Arthritis and Musculoskeletal and Skin Diseases Advisory Council

Director, Extramural Program
National Institute of Arthritis and Musculoskeletal and Skin Diseases

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Chairman, National Arthritis and Musculoskeletal and Skin Diseases Advisory Council

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